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COMPUTATIONAL MODELLING OF THE BEHAVIOUR OF BIOMARKER PARTICLES OF COLORECTAL CANCER IN FECAL MATTER

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Abstract. Colorectal adenocarcinoma is one of the carcinogenic diseases that is increasing the morbidity and mortality rates worldwide. The disease initially occurs through the segregation of biomarker substances in the human system without manifesting symptoms that affect the health of the carrier. Early detection would allow the application of more effective treatments, less invasive procedures and reduce the development of cancer. The purpose of this investigation was the elaboration of a mathematical model and the development of computational simulations to visualize the behavior of biomarker particles in transit through the colon. The flow conditions, properties of the viscous medium and biological regions of interest were established. Constitutive models, numerical conditions and solution strategies were determined. A numerical grid was used to represent the model of the colon and the human feces that carry the bioparticles (biomarkers). The results indicated the trajectories of the bioparticles in the fecal mass and the interactive movement with the natural contractions of the colon. The analysis of the movement of the biomarker particles can provide future less invasive alternatives for the detection in real time of the cancer by means of the implantation of biosensors in the walls of the colon.

1 INTRODUCTION

Worldwide, colorectal cancer (CRC) is one of the most frequently diagnosed degenerative diseases in the population [12, 10]. Despite the fact that some countries have improved their preventive systems for the detection of the disease, a high morbidity and

mortality rate persists due to late detection factors. [20, 18, 17]. In Colombia, for the year 2012, the CRC ranked fourth (7.8 %) in the estimated number of cases of incidence, being also the third cause of death (8.5 %) associated with cancer for both sexes. Globally, however, the CRC ranked third (9.7 %) in the estimated number of incident cases and fourth (8.5 %) in the estimated number of death cases [19, 17].

CRC generally develop as a result of neoplastic progression from adenomas into adenocarcinomas, which are defined as neoplasia derived from the lining of the gut. It is widely accepted that this transformation is triggered by the accumulation of both genetic and epigenetic alterations. The progression from an adenoma to carcinoma may take decades, which provides an opportunity for early CRC detection. Mass screening would therefore greatly contribute to the early diagnosis and timely treatment of CRC [7]. On account of that it is known that CRC develops from the accumulation of genetic and epigenetic changes in the epithelial cells of the colon, molecular markers directed to genetic alterations in tumor tissues and peripheral blood have been evolved [8].

Several research groups have developed mathematical modeling and computational simulations specifically to predict the growth of the advanced middle stage tumor, as well as to study the generation of metastases during different periods of the disease in the patients [3, 6].

Large intestine is composed of six representative parts: Cecum and apendix, ascending colon, transverse colon, descending colon, sigmoid colon and rectum. Rectum was selected to perform the analysis due its easier and more secure access in case of insert a measuring device. A complete reference image is provided in Figure 2 to identify the colorectal zone selected in this research.

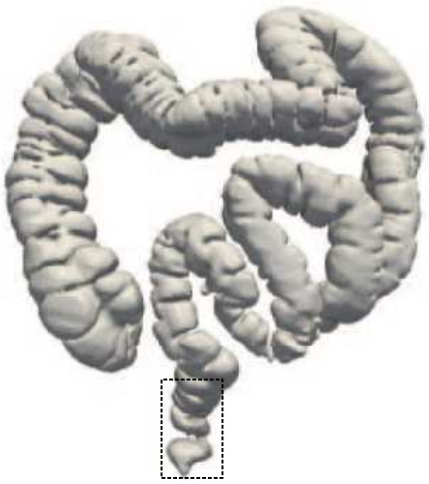

Figure 1: Complete 3D colon image and colorectal analysis section. Taken from [1]

2 MATERIALS AND METHODS

2.1 Definition of the study region

The gastrointestinal tract comprises of several distinct organs in sequence, extending over 7 meters in the human abdomen [13]. In this paper, a biological region of interest has been selected: colorectal section.

The colorectal region is composed of the walls of the colon that transport the fecal viscous mass inside. Based on the above description, a three-dimensional geometric model was constructed to represent the shape of the colorectal region for the development of the required studies. In the elaborated model, the folds and the biological diametral changes of the intestinal area were considered and the dimensions and radiuses obtained clinically indicated were incorporated.

2.2 Determination of biomaterials in colorectal region

The large intestine performs complex biological processes, such as: the absorption of fluids, electrolytes and vitamins, and the evacuation of fecal material [14]. The biomechanical properties and the geometric shape of the colon directly affect the proper behavior of this biological organ. Different models used to characterize the biomechanical properties of the walls of the intestine have been found, especially models of elastic-linear behavior, however in this investigation, a model of hyperelastic Neo-Hookean material of non-linear behavior was determined, since it would allow to reach a similarity with the natural peristatic movement of the organ. The mathematical model of the material implemented was:

$$W = \frac{\mu}{2}(\bar{I}_1 - 3) + \frac{1}{d}(J-1)^2 \tag{1}$$

It is the simplest form of deformation potential that exists for hyperelastic materials. The Neo-Hookean model allows to properly characterize the behavior of the material. Initial values of values of $\mu = 27104\ Pa$ and $d = 1.499e-7\ Pa^{-1}$ were implemented. This model requires the shear modulus and can only be subjected to uni-axial tension with deformation values ranging between 30% and 40%, and pure shear stresses with values of deformation ranging between 80% and 90%.

Human stool is modeled as a high viscous mass that is transported by peristaltic wave and physical parameters [11] were defined in table 1.

Table 1: Stool parameters.

Parameter	Symbol	Value	Unit
Density	μ	1060.00	kg/m^3
Viscosity	ν	5.00	Pa s

2.3 Biofunctionality conditions

There are several motor patterns that ensure that movements and propulsion are appropriate for the breakdown of food, absorption of nutrients and excretion of waste. These movements (peristalsis) are due to coordinated contractions and relaxations of circular and longitudinal smooth muscle layers [13].

Peristaltic movements in rectum allows to transport the waste to store it before the excretion process. Travelling peristaltic waves are generated in the intestinal wall and travel in the antegrade direction. The wave consists of contraction and relaxation components that modify the instantaneous wall tensions in each longitudinal slice [13]. This motion may be mathematically modeled as:

$$h(z,t) = a - 0.5\phi\left[1 + cos\frac{2\pi}{\lambda}(z - ct)\right]. \tag{2}$$

Where z, t, a, ϕ, λ, c y h are respectively axial coordinate, time, radius of the tube, amplitude of wave, wavelength, wave-speed and radial displacement of the walls from the center line [16].

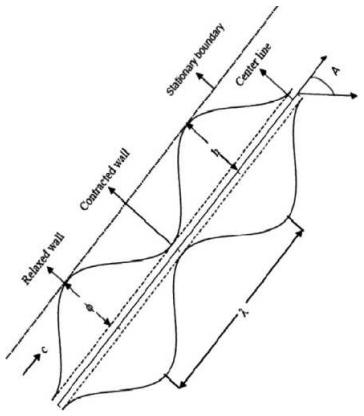

Figure 2: Radial displacement of the colon walls from the central line. Taken from [16].

A peristaltic wave was modeled in order to represent the pressure that travels along colorectal wall and whose function is transport stool during 6 seconds of simulation. Peristaltic pressure wave was plotted to represents its behavior with a pression value of 1893.17 Pa in figure 3 according to several intraluminal pressures reported in [2, 9, 4]:

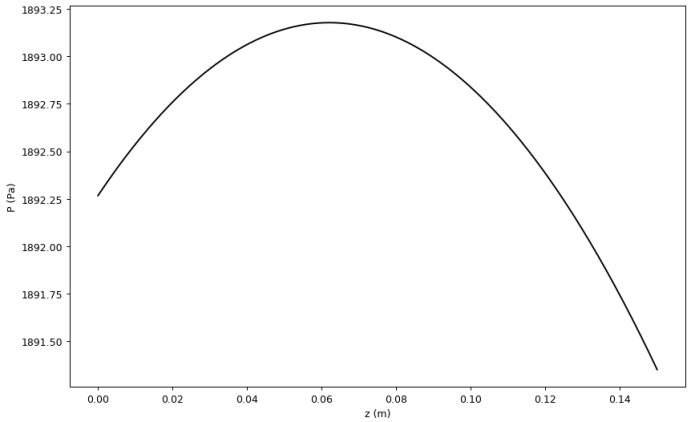

Figure 3: Pressure distribution on the entire wall (0.15 m) at t = 6.0 s.

2.4 Mesh configuration of region

The hexahedric configuration element was defined as the most adjusted and functional to represent the behavior of the biostructure. It was also considered that the eight-node hexahedral element met the physical and numerical conditions to represent the phenomenon. A mesh was constructed for the fluid and a mesh for the structure independently. The overall process of meshing was complex because of the particular shape of the colon (see fig 4). The dimensions chosen corresponds to 15 cm of length and a max diameter of 7 cm.

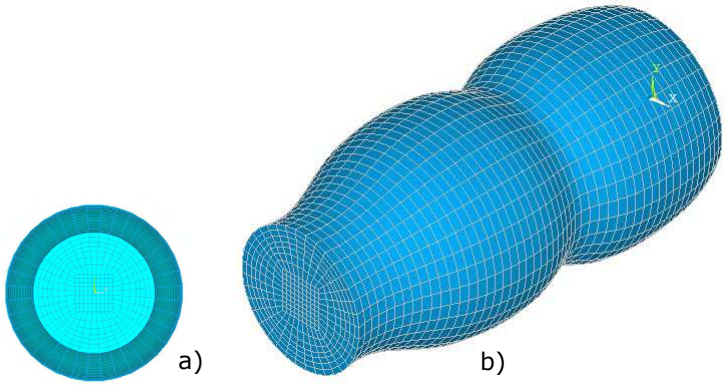

Figure 4: Geometric model meshed inside (fecal material) and in the structure (correctal surface). a) Front view of the geometry, b) perspective view of the geometry.

3 RESULTS AND ANALYSIS

Next, the results that indicate the dynamic behavior of the bio structure are presented, considering the peristaltic pressure, properties of the fecal matter and the characteristics and properties of the colorectal surface. Figure 5 represents the large deformations that occur in the dynamics of the phenomenon in three timesteps (t = 0.5, 2.0 and 6.0 seconds)

giving as a maximum value of radial displacement 6.34e-3 m. We observed a push behavior generated by the peristatic wave on the walls co-assisted by the geometric shape of the colon. There is evidence of an ease of mass displacement due to the biostructural form to the interior, which is formed by a folds and a diametrial variability, which favors the pushing force:

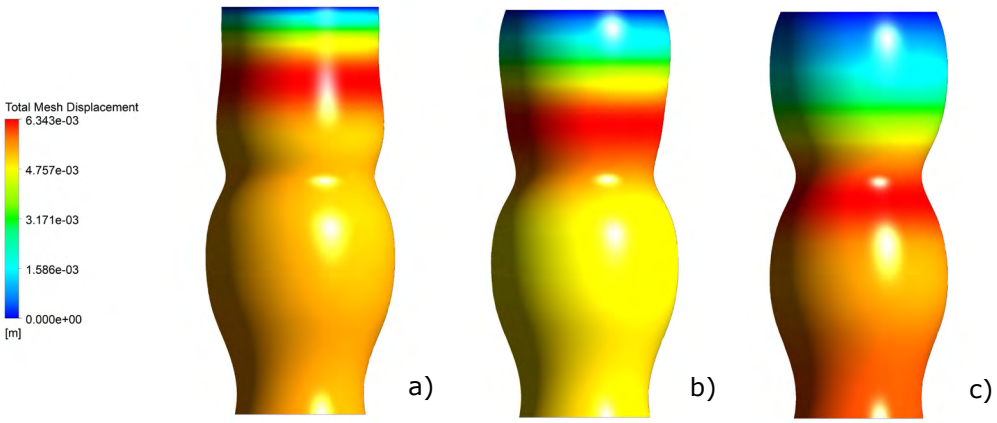

Figure 5: Total mesh displacement due to peristaltic wave in colorectal section at a) 0.5 seconds, b) 2.0 seconds and c) 6.0 seconds.

The behavior of the biological mass inside the colorectal model and the generation of mass flow orientation in time: 0.5, 2.0, 6.0 seconds, with maximum velocity values of 3.5e-3 m/s are presented in figure 6. The results indicated a random movement of the fecal mass into the colon where the greatest dynamic activity towards the inner wall of the colon occurs in some moments of greater compression, which would facilitate the capture of indicator particles of the colorectal disease. This behavior of greater pressure and speed towards the inner walls of the colon is the one of greater interest in the present investigation.

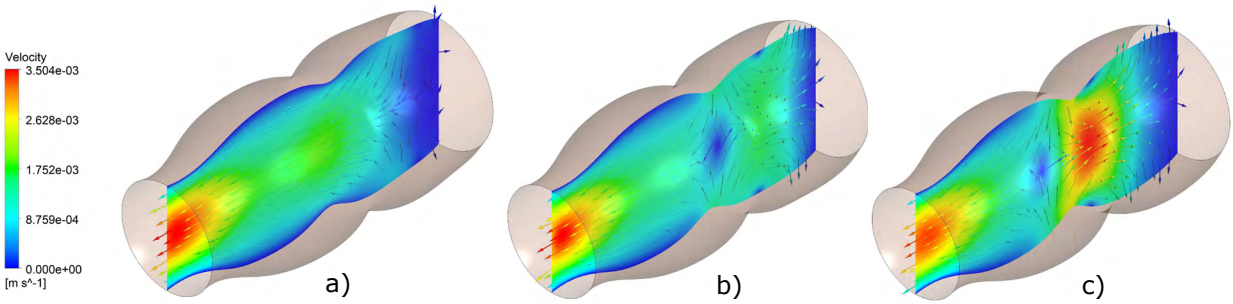

Figure 6: Stool velocity results by peristaltic wave in rectal section at a) 0.5 seconds, b) 2.0 seconds and c) 6.0 seconds.

In order to analyze the magnitude and direction of the mass flow, three cross sections were established, whose generated planes allow the estimation of the flow passing through

them. The first plane, located 0.01785 m from the inlet boundary, presents a flow that goes to the outlet boundary during the first 1.5 seconds, however, after 2 seconds, its direction changes towards the inlet boundary as can be observed in the figures 7-a, having as a maximum recoil value a positive mass flow of $1.3e-3$ kg/s. In the figures 6-b and 6-c, the vector field points in the sense of inlet boundary. It is important to note that as the time progresses, the magnitude of the mass flow begins to decrease after 3 seconds, which indicates that in the time after the second 6 could change the direction of flow again.

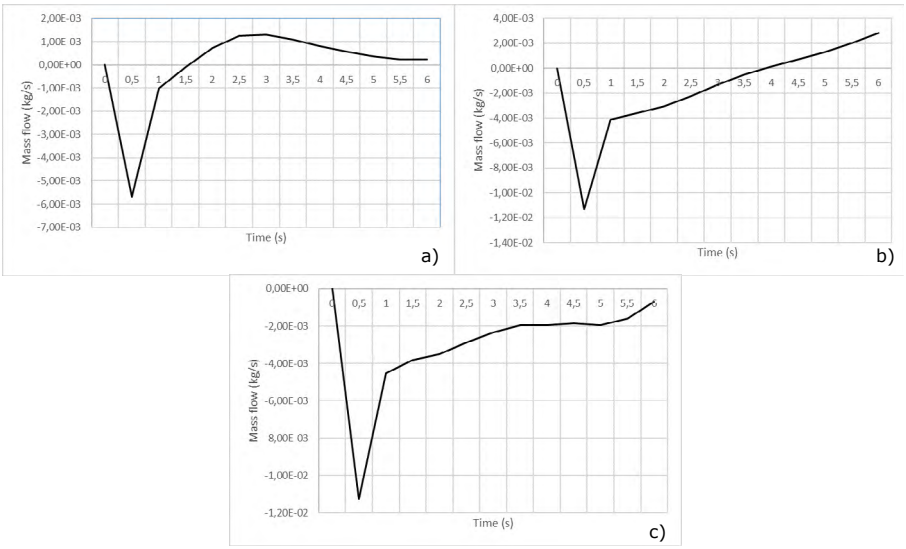

Figure 7: a) Mass flow through transversal slice plane at 0.01785 m of rectal inlet. b)Mass flow through transversal slice plane at 0.06 m of rectal inlet. c) Mass flow through transversal slice plane at 0.1137 m of rectal inlet. Simulation was performed during 6.0 seconds.

The second plane, located 0.06 m from the inlet boundary, presents a flow in the direction of outlet for a longer time, however, it also presents a backward movement from the second 4, as can be seen in the figure 7-b. In the figure 6-b (2 seconds), a significant decrease in the velocity of the flow can be identified because the system is approaching the instant in which the flow changes direction. The flow value for the plane analyzed at time t = 2 corresponds to $-3.07e-3$ kg/s in the direction of outlet.

The third plane, located 0.1137 m from the inlet boundary, has a flow in the direction of outlet permanently, as can be seen in the figure 7-c. However, a small decrease in velocity is noted, which could become a setback at the time of maximum pressure caused by the peristaltic pressure wave at that location.

4 CONCLUSIONS

- The Neo-Hokean model was appropiate to interact with pressure wave and it allowed an adequate displacement of the fecal mass, obtaining as a result the vector field of velocities in which the biomarker particles would be contained.

- Mass flow analized presents the backward behavior expected acording to pressure

wave applied. This behavior provides information about vector field direction and sense, and it allows identify the most interesesting region, which is located in the narrowest zone where highest velocities were found.

- The present research provides a significant contribution to the knowledge of the behavior of the fecal mass flow that contains biomarker particles for the search of early detection mechanisms, such as a possible implantation of a biosensor on the high contact areas.

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